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A Biological Unified Field Theory

Genes & Signals
By Mark Ptashne and Alexander Gann
Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press (2001). 208 pp. $59.00

Recall the days of yesteryear when, for biologists, enzymes were enzymes and didn't need any help in finding their substrates. Alas, those simple times are long gone. Instead we are faced with the horrible realization that proteins rarely see their ligands without being led by the nose to them. So, for example, RNA polymerase once promptly landed on a promoter and revved up to transcribe a gene. It turns out, in fact, that for most promoters, RNA polymerase requires additional proteins just to find the site. And other proteins interfere with its attachment. The number of such auxiliary factors, especially in eukaryotes, is mind boggling, and they are all tagged with impossible-to-decipher acronyms—usually several for the same factor. The situation is scarcely better in signal transduction. A hormone can only relay its message to the nucleus via passage through a long series of proteins, most of which have to be spatially constrained to transmit the signal. Even the simple matter of removing a piece of unwanted RNA from a transcript involves the assembly of a dozen or so proteins and RNAs, probably in a configuration that is highly specific. The reason for all this is now quite clear. Transcription cannot be ubiquitous, but is regulated by factors that respond to cellular environment, cell type, phases of the growth cycle, etc. Similarly, transduced signals are not sprayed around the cell, but are channeled toward specific effectors, as determined by the special requirements of the cell at a particular point in time.

Ptashne and Gann have made a bold and not altogether unsuccessful attempt to unify regulatory mechanisms into a few—perhaps one—principal scheme. They propose that what they term "recruitment" can explain most biochemical reactions that entail assemblies of proteins and other macromolecules. That is, that the surfaces of proteins that interact to form complexes are more or less like Velcro, and that the role of such surfaces is simply to stick together. A pair of interacting surfaces can be replaced by another pair, and the same end is accomplished—bringing the proteins together in a biologically relevant fashion. Their argument rests heavily on exactly such "domain-swapping" experiments. Consider an activator protein that consists of a DNA binding domain and an activator domain that adheres to RNA polymerase. The protein can be substituted for by a novel chimeric protein with a domain that binds near the promoter and an activating surface that can interact with RNA polymerase, Similarly, the interacting RNA polymerase subunit may not be critical. This notion is the basis of the yeast two-hybrid systems, which detect just such interacting protein faces (R. Brent and M. Ptashne, Cell *43*, 729–736, 1985).

Is this a case of reductionism ad absurdum? Protein assemblages do things that are regulatory in nature, i.e., transcription regulation can occur after proteins are assembled into complexes. These reactions include acetylation and deacetylation of histones, chromosome remodeling, etc. The authors are, of course, aware of this, and have broadened their use of the word "recruitment" to include, for example, the role of the lambda CI repressor in stimulating transcription at the phage Prm promoter. RNA polymerase binds readily to Prm, but fails to form an open complex (melt the DNA). Increasing the local concentration of RNA polymerase does not activate Prm. However, CI bound at a nearby site allows open complex formation. It drives the reaction toward the productive complex, presumably by stabilizing an intermediate in its formation. The interacting faces of CI and RNA polymerase are known, thanks to earlier work by Ptashne, but the fine molecular details of the reaction are not. Is this recruitment?

But why all this *pilpul* over a single word! Let's forget about it and move onto the meat of the book itself. Ptashne and Gann have written a clear and intelligent distillation of the various assembly pathways, especially in transcription initiation.

The authors start with the simplest systems, phage and bacteria, and work toward the more complex. They describe three types of activator-dependent transcription initiation in bacteria. In one, the activator and RNA polymerase bind weakly near the promoter, but their cooperative interaction stabilizes the binding. These interactions are not specific; any protein that bound near RNA polymerase and presented an interacting surface to it would suffice. In a second pathway, RNA polymerase is already stably bound to the promoter but is inactive. The activator, e.g., NtrC, contacts the bound polymerase and pushes it into a productive form. In this mechanism, in contrast to the first, the reaction between the activator and RNA polymerase is specific and informative: NtrC presumably induces an allosteric change in the bound polymerase. In a third system, the polymerase is bound at the promoter, but the DNA is improperly configured. An activator, e.g., MerR, binds the DNA and twists it, aligning the -10 and -35 regions. Of these three, according to Ptashne and Gann, the first, which exemplifies recruitment, is the most widely employed in nature to promote transcription initiation.

From phage and bacteria, Ptashne and Gann move on to yeast. They concentrate principally on GAL1 gene regulation, concluding, appropriately, that it is better to explore one system in depth than many systems superficially. And the control of GAL1 by Gal4 and other factors is sufficiently complex to serve as a model for many different types of promoter-activator or promoter-repressor interactions. They marshal additional evidence for simple adherence in Gal4 regulation of GAL1 transcription. Thus, mutations that enhance activation increase the negative charge of the activator domain or its size. These results argue against specific interactions between Gal4 and other members of the basal transcription apparatus. On the other hand, Ptashne and Gann caution about over-interpretation of these experiments. Although simple tethering can activate gene expression, it does not necessarily mean that the natural system behaves in a similar fashion. And the converse can be true as well; the artificial interacting surfaces may fail to align properly the components of the transcriptional

machinery. I guess we won't know for sure until the structure of a transcription initiation complex is solved, and we can visualize the interacting components. Gal1 also gives the authors a way to segue into the concept of sequential recruiting. Thus, the initial activators of a gene may change its epigenetic properties, e.g., by nucleosome remodeling, so that it attracts secondary activators.

Onward to higher eukaryotes and a variety of regulatory pathways. To show directly that mechanisms described in yeast are functional in higher organisms, the authors point out that Gal4 functions quite well as an activator in *Drosophila*. The differences between yeast and multicellular organisms are also described. For example, the proportion of histone that is acetylated in mammals is lower than in yeast, but acetylation is concentrated near active genes. A regulatory mechanism that allows polymerase stalled a short distance from the promoter to continue transcription in response to regulatory factors may be unique to higher organisms. And DNA methylation is not found in yeast, but serves an important regulatory role in more advanced eukaryotes. In a final burst of synthesis, Ptashne and Gann propose that signal transduction, RNA splicing, cell cycle control, and proteolysis can all be understood by the principle of recruitment.

So what is the value of this book? It explains complex biological reactions in terms of a few simple principles. Even if recruitment is often a heuristic device, it does focus one's attention on the essentials. A major strength of *Genes & Signals* is the spare use of experimental detail. An experimental approach is described briefly, e.g., crosslinking, and the results of the experiment and its implication for the biochemistry of the reaction under study are stressed. This approach is highly successful and the inverse of more conventional presentations, where experimental detail is laboriously elaborated and the conclusions to be drawn given short shrift. The artwork, by the way, is a pleasure. RNA polymerase, all pink and rubbery, drapes itself over the promoter, reaching out promiscuously to touch various partners. The book is also laced with higher order syntheses derived from the conclusions of individual experiments. Asking why activators are rarely found free of inhibitors in the nucleus, except when they are working appropriately, Ptashne and Gann propose that this keeps the activator concentration from reaching a level where transcription in general would be squelched. And the same argument could be made for nuclear repressors.

Because of the clarity and logic of the presentation, *Genes & Signals* can be recommended for a very wide audience, from college students to experienced researchers. It is not long, it's fun, and it makes you think.

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Fighting HIV/AIDS

Staying Alive
By Fran Balkwill and Mic Rolph
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Less than a decade after the fall of apartheid, South Africa is faced with the largest and most rapidly growing HIV/AIDS epidemic in Africa and in the world. In South Africa, over 4.7 million people, or one in four adults, are currently thought to be living with HIV/AIDS. At present, this number is higher than in any other country in the world and is expected to double over the next decade.

The salient characteristics of the epidemic are threefold: (1) Explosive in nature; most information has been based upon seroprevalence studies in antenatal clinics. These show steeply rising rates of HIV infection from less than 1% in 1991 to over 30% in 2000. In the most heavily affected province, KwaZuluNatal, the latest figures show a prevalence rate of 36% among antenatal clinic attendees and an annual incidence rate of 20%. (2) Predominant heterosexual transmission with higher rates and lower age among women; estimates indicate that 60% of infections are in women and the median infection age among women is 22 years, whereas it is 30 years among men, an indication of a pattern of older men having sex with younger women. Most experts believe that about 85% of infection is through heterosexual transmission, 10% through mother-to-child transmission, and the remaining 5% through same-sex transmission, intravenous drug use, and occupational exposure. As corollaries, there are very high rates of perinatal infections, a growing population of infected and affected children, and a frightening pattern of sexual violence. (3) Enormous and rapidly growing burden of HIV disease. The South African Medical Research Council estimates that 7 million people will likely die by 2010. The total population of South Africa is about 40 million. In US population terms, that would be the equivalent of death of over 30 million Americans. It is estimated that by 2005, only 13% of the South African population would live to celebrate their fortieth birthdays, if these current trends continue. A very telling statistic is that over 25% of nursing students are thought to be already HIV infected, and it is estimated that that proportion will reach 40%–50% during the next decade. The high prevalence of infection and consequent expected mortality has begun to have widespread social and economic effects. For example, large numbers of orphans are now present, and there will be many more. In addition, certain vital community service workers, such as teachers and nurses, are ill and dying, causing disruption of essential educational and health infrastructures. This problem is now reaching full force.

There is no single explanation for the explosive nature of the epidemic. It is likely a result of a confluence of social, behavioral, and biological forces. Among these are: (1) the residual social patterns of colonialism and apartheid, which disrupted traditional social structures, producing forced racial and economic separation and